



(11) **EP 1 948 142 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
09.04.2014 Bulletin 2014/15

(51) Int Cl.:
A61K 9/70 (2006.01) A61L 15/58 (2006.01)

(21) Application number: **06815388.1**

(86) International application number:
PCT/US2006/037341

(22) Date of filing: **22.09.2006**

(87) International publication number:
WO 2007/035939 (29.03.2007 Gazette 2007/13)

(54) **HIGH ENHANCER-LOADING POLYACRYLATE FORMULATION FOR TRANSDERMAL APPLICATIONS**

POLYACRYLATFORMULIERUNG MIT HOHER BELADUNG VON VERSTÄRKENDEN
SUBSTANZEN FÜR TRANSDERMALE ANWENDUNGEN

FORMULATION DE POLYACRYLATE SUPERIEUR AVEC CHARGEMENT D'ACTIVATEUR
DESTINEE A DES APPLICATIONS TRANSDERMIQUES

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR**

(30) Priority: **23.09.2005 US 720201 P**
30.09.2005 US 723135 P

(43) Date of publication of application:
30.07.2008 Bulletin 2008/31

(60) Divisional application:
11152742.0 / 2 308 480

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Description

TECHNICAL FIELD

5 **[0001]** This invention relates to transdermal drug delivery using a formulation having a polyacrylate. In particular, the invention relates to adhesive systems with polyacrylate having high enhancer and drug tolerance when used in transdermal drug delivery.

BACKGROUND

10 **[0002]** Transdermal devices for the delivery of biologically active agents have been used for maintaining health and therapeutically treating a wide variety of ailments. For example, analgesics, steroids, etc., have been delivered with such devices. Such transdermal devices include patches in which a biologically active agent is delivered to the body tissue passively without use of an additional energy source. Many such devices have been described, for example, in U.S. Pat. Nos. 3,598,122, 3,598,123, 4,379,454, 4,286,592, 4,314,557, 4,568,343, and U.S. Application No. 2003002682.

15 **[0003]** A transdermal patch is typically a small adhesive bandage that contains the drug to be delivered. A simple type of such transdermal patches is an adhesive monolith including a drug-containing reservoir disposed on a backing. The reservoir is typically formed from a pharmaceutically acceptable pressure sensitive adhesive. In some cases, the reservoir can be formed from a non-adhesive material, the skin-contacting surface of which is provided with a thin layer of a suitable adhesive. The rate at which the drug is administered to the patient from these patches can vary due to normal person-to-person and skin site-to-skin site variations in the permeability of skin to the drug.

20 **[0004]** Sometimes patches can be multilaminate or can include a liquid reservoir layer in the patches. A drug release-rate controlling membrane can be disposed between the drug reservoir and the skin-contacting adhesive. This membrane, by decreasing the release rate of drug from the patch, serves to reduce the effects of variations in skin permeability.

25 **[0005]** Although the transdermal delivery of therapeutic agents has been the subject of intense research and development for over 30 years, only a relatively small number of drug molecules are suitable for transdermal delivery due to the fact that human skin is an excellent barrier. Various techniques have been explored to enhance the permeation of drug molecules that are not otherwise suitable for transdermal delivery. Of these techniques, chemical enhancement is the most established and is currently employed commercially. Pressure sensitive adhesives, such as acrylic adhesives, are used in most transdermal drug delivery devices as a means of providing intimate contact between the drug delivery device and the skin. The use of enhancers, especially at high concentrations, usually has a significant impact on the properties of pressure sensitive adhesives, such as cohesive strength, adhesive flow, tackiness and adhesion strength. Therefore, pressure sensitive adhesives have to be designed in a way that they can provide the needed performance in the presence of enhancer.

35 **[0006]** Many systems with adhesives and permeation enhancers have been described in the past, e.g., U.S. Pat. Nos. 3,558,574; 4,554,324; 4,822,676; 5,573,778, and 6,077,527. Some discussed the use of grafting macromers to the backbone (U.S. Pat. Nos. 5,573,778). Some discussed cross-linking (U.S. Pat. No. 6,077,527). EP 1369112 concerns a percutaneous absorption-type pharmaceutical preparation which comprises a pressure sensitive adhesive crosslinked with a release rate of drug from the patch, serves to reduce the effects of variations in skin permeability.

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50 **[0008]** Many systems with adhesives and permeation enhancers have been described in the past, e.g., U.S. Pat. Nos. 3,558,574; 4,554,324; 4,822,676; 5,573,778, and 6,077,527. Some discussed the use of grafting macromers to the backbone (U.S. Pat. Nos. 5,573,778). Some discussed cross-linking (U.S. Pat. No. 6,077,527). However, at the present, there does not seem to be systems that have high enhancer and drug tolerance and yet provides pressure sensitive adhesive property.

55 **[0009]** EP 1639999 discloses a nonaqueous pressure-sensitive adhesive for a medicinal tape preparation for percutaneous absorption comprising a support, a pressure-sensitive adhesive layer containing a drug and a nonaqueous pressure-sensitive adhesive, and a release film. The adhesive may comprise a copolymer obtained by copolymerization of a (meth)acrylic monomer having an acetoacetyl group and one or more monomers from among other (meth)acrylic

monomers without acetoacetyl groups and copolymerizable vinyl monomers.

[0010] WO 96/08229 discloses a transdermal drug delivery device, comprising a backing and a matrix adhered to one side of the backing. The matrix is formed from a copolymer comprising one or more monomers selected from the group consisting of alkyl (meth)acrylates containing 4 to 10 carbon atoms in the alkyl group, and optionally one or more ethylenically unsaturated monomers copolymerizable with the alkyl(meth)acrylate, and a macromonomer copolymerizable with the other monomer(s) and having a molecular weight in the range 500-500,000. The matrix further comprises a softener dissolved in the copolymer, and if the softener is not therapeutically effective, a therapeutically effective amount of a drug.

[0011] There continues to be a need for improved transdermal systems, especially transdermal systems that can deliver pharmaceutical agents with a high load of pharmaceutical agents and/or permeation enhancers and yet provide desirable pressure sensitive property.

SUMMARY

[0012] The present invention provides a device for transdermal delivery of biologically active agent or agents for therapeutic effects, especially delivery of the biologically active agents to a subject through skin or other body surface that is accessible from exterior without using endoscopic devices, and method of making a reservoir for such a device. An individual can wear the device over an extended period of time.

[0013] The device is defined in the appended claims. Subject-matter which is not encompassed by the scope of the claims does not form part of the present invention.

[0014] In one aspect, the present invention provides a transdermal system having improved enhancer loading, little or no cold flow, with desirable tack and adhesion.

[0015] In another aspect, the present invention relates to a transdermal system in which pharmaceutical properties, in particular, enhancer tolerance, is optimized by controlling the rheological properties of the polyacrylate material.

[0016] In one aspect of the invention, a novel technique is provided for increasing adhesive enhancer tolerance. Specifically, it has been discovered that by increasing the glass transition temperature of the acrylate polymer using the ratio of soft monomer and hard monomer, it is possible to load enhancer concentrations into the polymer at a high weight percent to obtain a formulation and still achieve desirable adhesive characteristics. It is possible to load drug and/or enhancer into the polymer composition to a high concentration, e.g., at greater than 20 dry weight %, greater than 30 dry weight % (or solids wt%), even up to 40 - 50 wt%, without adversely impacting the adhesion and rheological characteristics for pressure sensitive adhesive (PSA) application. With sufficient loadings of permeation enhancers in such formulations, sustained high rates of drug delivery can be achieved. With adequate adhesive properties, the resulting reservoir with sufficient drug loading and permeation enhancers can be used for effective therapeutic results. Prior to incorporation of drugs and ingredients, the polymeric materials are not suitable PSAs "as is" because of the stiffness of the polymer and insufficient adhesiveness or tackiness. These polymeric materials become adhesive and have the desired PSA characteristics after incorporating drug, permeation enhancer and optionally other ingredients in suitable quantities. Such polymeric materials, which are not suitable as a PSA as is (prior to incorporation of drugs and ingredients) but will have the desired PSA characteristics after incorporating drugs and/or other ingredients, can be called "proadhesive" herein.

[0017] In one aspect, the bandermal drug delivery device of the present invention has a reservoir including at least one drug, permeation enhancer and an acrylate polymer, wherein the acrylate polymer has no more than 60 wt% soft monomer, has at least 40 wt% hard monomer and 10 to 40 wt% polar functional monomer, the acrylate polymer constituting 45 wt% to 80 wt% of the reservoir. The acrylate polymer can have dissolved in it at least 30 wt% of the drug and permeation enhancer combination. The acrylate polymer has a T_g of greater than -15°C if without permeation enhancer and without drug. With drug and enhancers dissolved therein, the reservoir has pressure sensitive adhesive properties applicable to the body surface for transdermal delivery.

[0018] In another aspect, the present invention provides methods of making such transdermal drug delivery devices.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019]

FIG. 1 illustrates a cross-section through a schematic, perspective view of one embodiment of a transdermal therapeutic system according to the present invention.

FIG. 2 illustrates a cross-section view through another embodiment of a transdermal therapeutic system of this invention.

DETAILED DESCRIPTION

[0020] The present invention relates to transdermal delivery of pharmaceutical agents to a patient in need thereof involving the use of an acrylate polymer material that after incorporating drug(s) and other ingredients therein can act

as a pressure sensitive adhesive (PSA) and maintain the Transdermal delivery system on a body surface of an individual. **[0021]** A pressure sensitive adhesive (PSA) is a material that adheres with light pressure, is aggressively and permanently tacky, exerts a strong holding force, and should be removable without leaving a residue. Pressure sensitive tack is the property that enables an adhesive to form a bond with the surface of another material upon brief contact under light pressure (usually no more than applied finger pressure). To achieve pressure sensitive tack, adhesives have to be easily deformed at the time scale allowed for bond formation, usually on the order of a fraction of a second. Besides tack, cohesive strength is desirable in transdermal uses to reduce the mass transfer of adhesive to the skin when the patch is removed. Resistance to cold flow is also desirable to prevent the adhesive from oozing from the patch during storage and use. It was found that the glass transition temperature, creep compliance (J), and elastic modulus (G') at the application temperature are important requirements for pressure sensitive adhesive performance.

[0022] Traditionally a transdermal drug delivery system was formulated with a pressure sensitive adhesive that has a glass transition temperature (T_g) in the range of -40°C to -10°C. According to the present invention, the starting acrylate polymeric material (which can be formulated into an adhesive material having pharmaceuticals (or drugs) and/or enhancers) has a glass transition temperature (T_g) in the range of about -15°C or higher, more preferably -15 °C to 0 °C, and even more preferably -10 °C to 0 °C; creep compliance of about 7×10^{-5} cm²/dyn (at 3600 second) or below, and modulus G' of about 8×10^5 dyn/cm² or above. The polymeric material can be formulated into a transdermal reservoir matrix (including carrier structure) with a combined drug and/or enhancer concentration greater than 30 dry weight percent (wt%), or even greater than 40 dry weight percent. The resulting transdermal adhesive formulation with drug agent(s) and/or enhancers will provide excellent adhesion with no cold flow, i.e., with no cold flow of an amount that is noticeable and would affect the normal use of the delivery system. By contrast, the starting proadhesive acrylate polymer has poor adhesive properties because the glass transition temperature is too high. Once plasticized in the transdermal formulation, the glass temperature drops into the pressure sensitive range, about -10 to -40° C, and the resulting creep compliance and storage modulus enables the achievement of good tack, with little or no cold flow. Creep compliance is an important parameter to evaluate cold flow behavior of a pressure sensitive adhesive (PSA). In a transdermal drug delivery system, if the creep compliance is large, the adhesive will have cold flow with time, i.e., the adhesive may lose its shape just because of the weight of the material in the device under gravity.

[0023] In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below. As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the text content clearly dictates otherwise.

[0024] As used herein, the term "transdermal" refers to the use of skin, mucosa, and/or other body surfaces as a portal for the administration of drugs by topical application of the drug thereto for passage into the systemic circulation.

[0025] "Biologically active agent" is to be construed in its broadest sense to mean any material that is intended to produce some biological, beneficial, therapeutic, or other intended effect, such as enhancing permeation, relief of pain and contraception. As used herein, the term "drug" refers to any material that is intended to produce some biological, beneficial, therapeutic, or other intended effect, such as relief of symptoms of health disorder, but not agents (such as permeation enhancers) the primary effect of which is to aid in the delivery of another biologically active agent such as the therapeutic agent transdermally.

[0026] As used herein, the term "therapeutically effective" refers to the amount of drug or the rate of drug administration needed to produce the desired therapeutic result. As used herein, the term "permeation enhancement" intends an increase in the permeability of skin to a drug in the presence of a permeation enhancer as compared to permeability of skin to the drug in the absence of a permeation enhancer. A "permeation-enhancing amount" of a permeation-enhancer is an amount of the permeation enhancer sufficient to increase the permeability of the body surface of the drug to deliver the drug at a therapeutically effective rate.

[0027] "Acrylate", "polyacrylate" or "acrylic polymer", when referring to a polymer for an adhesive or proadhesive, refers to polymer or copolymer of acrylic acid, ester(s) thereof, acrylamide, or acrylonitrile. Unless specified otherwise, it can be a homopolymer, copolymer, or a blend of homopolymers and/or copolymers.

[0028] As used in the present invention, "soft" monomers refer to the monomers that have a T_g of about -80 to -10 °C after polymerization into homopolymer; "hard" monomers refer to the monomers that have a T_g of about 0 to 250°C after forming homopolymer; and "functional" monomers refer to the monomers that contain hydrogen bonding functional groups selected from hydroxyl, carboxyl or amino groups (e.g., alcohols, carboxylic acid, or amines), these polar groups tend to increase the hydrophilicity of the acrylate polymer and increase polar drug solubility.

[0029] Exemplary transdermal drug delivery systems of the present invention are illustrated by the embodiments shown in FIGS. 1 and 2. As shown in FIGS. 1 and 2, an embodiment of the transdermal monolithic patch 1 according to this invention has a backing layer 2, a drug reservoir 3 disposed on the backing layer 2, and a peelable protective

layer 5. In the reservoir 3, which can be a layer, at least the skin-contacting surface 4 is an adhesive. The reservoir is a matrix (carrier) that is suitable for carrying the pharmaceutical agent (or drug) for transdermal delivery. Preferably, the whole matrix, with drugs and other optional ingredients, is a material that has the desired adhesive properties. The reservoir 3 can be either a single phase polymeric composition or a multiple phase polymeric composition. In a single phase polymeric composition the drug and all other components are present at concentrations no greater than, and preferably less than, their saturation concentrations in the reservoir 3. This produces a composition in which all components are dissolved. The reservoir 3 is formed using a pharmaceutically acceptable polymeric material that can provide acceptable adhesion for application to the body surface. In a multiple phase polymeric composition, at least one component, for example, a therapeutic drug, is present in amount more than the saturation concentration. In some embodiments, more than one component, e.g., a drug and a permeation enhancer, is present in amounts above saturation concentration. In the embodiment shown in Fig. 1, the adhesive acts as the reservoir and includes a drug.

[0030] In the embodiment shown in FIG. 2, the reservoir 3 is formed from a material that does not have adequate adhesive properties if without drug or permeation enhancer. In this embodiment of a monolithic patch 1, the skin-contacting surface of the reservoir 4 may be formulated with a thin adhesive coating 6. The reservoir 3 may be a single phase polymeric composition or a multiple phase polymeric composition as described earlier, except that it may not contain an adhesive with adequate adhesive bonding property for skin. The adhesive coating can contain the drug and permeation enhancer, as well as other ingredients.

[0031] The backing layer 2 may be formed from any material suitable for making transdermal delivery patches, such as a breathable or occlusive material including fabric or sheet, made of polyvinyl acetate, polyvinylidene chloride, polyethylene, polyurethane, polyester, ethylene vinyl acetate (EVA), polyethylene terephthalate, polybutylene terephthalate, coated paper products, aluminum sheet and the like, or a combination thereof. In preferred embodiments, the backing layer includes low density polyethylene (LDPE) materials, medium density polyethylene (MDPE) materials or high density polyethylene (HDPE) materials, e.g., SARANEX (Dow Chemical, Midland, Mich.). The backing layer may be a monolithic or a multilaminate layer. In preferred embodiments, the backing layer is a multilaminate layer including nonlinear LDPE layer/linear LDPE layer/nonlinear LDPE layer. The backing layer can have a thickness of about 0.012 mm (0.5 mil) to 0.125 mm (5 mil); preferably about 0.025 mm (1mil) to 0.1 mm (4 mil); more preferably about 0.0625 mm (1.5 mil) to 0.0875 mm (3.5 mil).

[0032] The drug reservoir 3 is disposed on the backing layer 2. At least the skin-contacting surface of the reservoir is adhesive. As mentioned, the skin-contacting surface can have the structure of a layer of adhesive.

[0033] The reservoir 3 is formed from a pharmaceutically acceptable acrylate adhesive or proadhesive, as described in greater detail below. The drug reservoir or the matrix layer can have a thickness of about 1-10 mils (0.025- 0.25 mm), preferably about 2-5 mils (0.05-0.12 mm), more preferably about 2-3 mils (0.05-0.075 mm).

[0034] The materials for making the adhesive reservoir or adhesive coating, and especially for making proadhesives according to the present invention are acrylates, which can be a copolymer of various monomers ((i) "soft" monomer, (ii) "hard" monomer, and (iii) "functional" monomer) or blends including such copolymers. The acrylates (acrylic polymers) can be composed of a copolymer (e.g., a terpolymer) including at least two or more exemplary components selected from the group including acrylic acids, alkyl acrylates, methacrylates, copolymerizable secondary monomers or monomers with functional groups. Functional monomers are often used to adjust drug solubility, polymer cohesive strength, or polymer hydrophilicity. Examples of functional monomers are acids, e.g., acrylic acid, methacrylic acid and hydroxy-containing monomers such as hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamides or methacrylamides that contain amino group and amino alcohols with amino group protected. Functional groups, such as acid and hydroxyl groups can also help to increase the solubility of basic ingredients (e.g., drugs) in the polymeric material. Additional useful "soft" and "hard" monomers include ethyl acrylate, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, tridecyl methacrylate, methoxyethyl acrylate. Additional examples of acrylic adhesive monomers suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). Examples of acrylic adhesives are commercially available from National Starch and Chemical Company, Bridgewater, N.J.

[0035] The acrylate polymers can include cross-linked and non-cross-linked polymers. The polymers can be cross-linked by known methods to provide the desired polymers. However, cross-linking is hard to control and may result in polymeric materials that are too stiff or too soft. It is preferred that the polymeric material for incorporation of drugs and other ingredients to be polymer without crosslinking and no cross-linking agent is used in forming the polymeric material. It is further preferred that the monomers do not self cross-link during polymerization. In the present invention, it was found that, instead of cross-linking to form a matrix adhesive with desired PSA properties for incorporating drugs and enhancers, good control of the PSA properties can be achieved by selecting polymeric materials that are too stiff prior to incorporation of drugs and other ingredients and subsequently incorporating such drugs and ingredients. It has been found that an acrylate polymer composition with a creep compliance (J) of $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$ or below and elastic modulus

G' of 8×10^5 dyn/cm² or above, although too stiff as a PSA as is, after formulating with drug or enhancer or a combination thereof at a relative high concentration will achieve the desirable adhesive properties. The plasticizing or tackifying effect of the drug(s) and/or other ingredients on the polymeric material provides a means to achieve the desired adhesive properties in the reservoir.

[0036] Acrylate polymers, when the main monomer of which has the general formula $\text{CH}_2=\text{CH}-\text{COOR}$, are particularly useful as proadhesives. Typical main monomers are normally alkyl acrylates of 4 to 1 carbon atoms, preferably 4-10 carbons. Useful alkyl acrylates include ethyl acrylate, butyl acrylate, 2-ethylhexyl acrylate, with 2-ethylhexyl acrylate, butyl acrylate being preferred. Such "soft" monomers if polymerized into homopolymer generally have a T_g of less than about 0°C, preferably about -10°C to -80°C, preferably about 20°C to -80°C. Preferably, they are present in an amount of about 10 to 70 wt% (i.e., dry weight % or solids wt%), more preferably no more than about 60 % by weight, more preferably no more than about 50 wt% of the total monomer weight and more preferably about 40 to 50 wt%. As used herein, when a monomer is said to be present in the acrylate polymer at a certain percentage, it is meant that the monomer has been polymerized in the acrylate polymer at that percentage of polymerization monomer ingredients.

[0037] "Hard" modifying monomers are mainly used to modify the adhesive properties, mainly glass transition temperature (e.g., to increase the T_g and to make the resulting polymer stiffer at room temperature), to meet various application requirements. A hard monomer, if polymerized into homopolymer, has a T_g of about 0 to 250 °C, preferably about 20 to 250 °C, more preferably in the range of about 30 to 150°C (for convenience, this is referred to as the "homopolymer T_g " herein). The hard monomer component (or content in the polymer) is present in an amount of about 10 wt% or more, preferably in the range of about 30 to 60 wt%, preferably about 35 to 60 wt%, more preferably about 40 to 60 wt%, even more preferably about 40 to 50 wt% in the polymerization. Examples of hard modifying monomers are vinyl acetate, and substituted acrylamides. Homopolymers of these monomers generally have higher glass transition temperature than homopolymers of the soft monomers.

[0038] Certain nitrogen containing monomers can be included in the polymerization to raise the T_g . These include N-tertiary octyl acrylamide (t-octyl acrylamide)

[0039] Functional monomers can be used to either provide needed functionality for solubilizing agents in the polyacrylate or improve cohesive properties. Examples of functional monomers are organic acids, e.g., acrylic acid, and hydroxyl-containing monomers such as hydroxyethyl acrylate. Preferred functional monomers when incorporated into the polymer result in acid groups, i.e., -COOH, hydroxyl groups, i.e., -OH, or amino groups in the polymer for affecting the solubility of basic agents such as basic drugs. Examples of hydroxy functional monomers include hydroxyethyl acrylate. Useful carboxylic acid monomers to provide the functional group include, acrylic acid.

[0040] A functional monomer can also be a hard monomer, if its homopolymer has the high T_g . Such functional monomers that can also function as hard monomers include, e.g., hydroxyethyl acrylate and acrylic acid,

[0041] The functional monomer(s) are present in the acrylate polymer in an amount of 10 to 40 wt%, more preferably about 10 to 30 wt%, more preferably about 10 to 20 wt%, even more preferably 10 to 15 wt%, even though some of the functional monomer(s) may be hard monomers. Examples of preferred functional monomer component include acrylic acid and hydroxyethyl acrylate, acrylamides that contain amino group and amino alcohols with amino group protected. One of the applications of using functional monomers is to make a polar proadhesive having higher enhancer tolerance, in that, for example, the resulting PSA with the enhancers and/or drug will not phase separate or have excessive cold flow.

[0042] In certain embodiments, the hard monomer(s) that are not also functional monomer can constitute about 10 to 60 wt%, preferably about 40 to 60 wt% of the acrylate monomer, especially in cases in which no acidic functional hard monomer and less than about 20 wt% of hydroxyl functional hard monomer are included in the acrylate polymer. In other embodiments, the hard monomer(s) that are not also functional monomer can constitute about 5 to 15 wt%, e.g., about 10 wt% of the acrylate monomer, especially in cases in which a large amount (e.g., about 25 wt% or more) of functional hard monomer(s) are included, such as when more than about 5 wt% acidic hard functional monomers and 10 or more wt% (e.g., about 10-25 wt%) hydroxyl functional hard monomer(s) are included in the acrylate polymer.

[0043] Below is a table showing the T_g 's of exemplary soft and hard homopolymers the monomers of which are useful for making proadhesive of the present invention. Some of the monomers (e.g., acrylic acid, hydroxyethyl acrylate) are also functional monomers.

poly(hydroxyethyl acrylate) (hard/functional monomer)	around 100 °C
poly(acrylic acid) (hard/functional monomer)	106 °C
poly(vinyl acetate) (hard monomer)	30 °C
poly(ethylhexyl acrylate) (soft monomer)	-70 °C
poly(isopropyl acrylate) (soft monomer)	-8°C

(continued)

poly(n-propyl acrylate) (soft monomer)	-52 °C
poly(isobutyl acrylate) (soft monomer)	-40 °C
poly(n-butyl acrylate) (soft monomer)	-54 °C
poly(n-octyl acrylate) (soft monomer)	-80 °C

[0044] It has been found that the soft monomers 2-ethylhexyl acrylate and butyl acrylate are especially suitable to polymerize with functional monomers hydroxyethyl acrylate or acrylic acid either alone or in combination to form the acrylate polymer of the present invention. Further, the hard monomer vinyl acetate has been found to be very useful to polymerize with the soft monomers 2-ethylhexyl acrylate and butyl acrylate, either alone or in combination to form the proadhesive. Thus, the acrylate proadhesive polymer of the present invention is especially suitable to be made from 2-ethylhexyl acrylate or butyl acrylate copolymerized with hydroxyethyl acrylate, acrylic acid, or vinyl acetate, either alone or in combination. Another preferred hard monomer is t-octyl acrylamide, which can be used alone or in combination with other hard monomers such as acrylic acid and hydroxyethyl acrylate.

[0045] In an embodiment, the proadhesive is made by polymerizing monomers including about 30 to 75 wt% vinyl acetate, about 10-40 wt% hydroxyl functional monomer and about 10-70 wt% soft monomer such as 2-ethylhexyl acrylate or butyl acrylate. In a preferred embodiment, the proadhesive is made by polymerizing monomers including about 50 to 60 wt% vinyl acetate, about 10-20 wt% hydroxyethyl acrylate, and about 20-40 wt% 2-ethylhexyl acrylate. In some cases, no carboxyl (acid) group is used. Hydroxyethyl acrylate can be used to provide hydroxyl functionality. For example, one embodiment is a proadhesive having about 50 wt% vinyl acetate, about 10 wt% hydroxyethyl acrylate, and about 40 wt% 2-ethylhexyl acrylate. As used herein, when a specific percentage is mentioned, it is contemplated there may be slight variations, e.g., of plus or minus 5% of the specific percentage (i.e., about 10 wt% may include 10 wt% $\pm$ 0.5wt%). One other embodiment is a proadhesive having about 60 wt% vinyl acetate, about 20 wt% hydroxyethyl acrylate, and about 20 wt% 2-ethylhexyl acrylate.

[0046] In another embodiment, the proadhesive is made by polymerizing monomers including both monomer with hydroxyl group and monomer with carboxyl group. For example, certain preferred monomer combination for polymerization include an alkyl acrylate, an acrylamide, a monomer with hydroxyl group and a monomer with carboxyl group, e.g., making a proadhesive by polymerizing butyl acrylate, 2-hydroxyethyl acrylate, t-octyl acrylamide, and acrylic acid.

[0047] In certain cases for making a proadhesive in which both monomers with hydroxyl groups and monomer with carboxyl groups are to be polymerized with a soft monomer, e.g., butyl acrylate, the monomer proportions in the polymerization includes about 55 to 65 wt% soft monomer (e.g., butyl acrylate), about 5 to 15 wt% t-octyl acrylamide, about 20 to 30 wt% hydroxyethyl acrylate and about 5 to 10 wt% acid monomer such as acrylic acid. In one embodiment, the acrylate polymer includes about 59 wt% butyl acrylate, about 10 wt% t-octyl acrylamide, about 25 wt% hydroxyethyl acrylate and about 6 wt% acrylic acid.

[0048] It is important that with the incorporation of a large amount of permeation enhancers, the T_g of the resulting reservoir (with the drug, permeation enhancers and other ingredients) is such that the resulting reservoir would have good PSA properties for application to the body surface of an individual. Further, the resulting reservoir should not have cold flow that affects the normal application of the transdermal delivery. The acrylate polymer (or a blend of acrylate polymers) constitutes 45 wt% to 80 wt% of the reservoir. It is possible to load drug and/or enhancer into the polymer composition to a high concentration. For example, the permeation enhancer, with or without drug, can be at or greater than about 20 dry weight %, preferably at or greater than about 30 dry weight % (or solids wt%), even more preferably up to about 40 to 50 wt% of the drug delivery reservoir, without adversely impacting the adhesion and rheological characteristics for pressure sensitive adhesive (PSA) application.

[0049] Preferred acrylate polymers or blends thereof provide the acrylic pressure sensitive properties in the delivery system glass transition temperature of about -10 to -40°C, preferably about -20 to -30°C at application on a surface. The T_g of an acrylate polymer can be determined by differential scanning calorimetry (DSC) known in the art. Also, theoretical ways of calculating the T_g of acrylate polymers are also known. Thus, one having a sample of an acrylate polymer will be able to experimentally determine the T_g , for example, by DSC. One can also determine the monomer composition of the acrylate polymer and estimate theoretically the T_g by calculation. From the knowledge of the monomer composition of an acrylate polymer having drugs and enhancers, one can also make the acrylate polymer without the drug and enhancer and determine the T_g . According to the present invention, the acrylate materials, before dissolving the drug(s), permeation enhancers, etc., have T_g 's that are preferably in the range of about -15 to 10°C, and have rheological properties that are not quite suitable for use directly as a PSA to skin because of the stiffness of the material. The acrylate polymers preferably have a molecular weight in a range of about 200,000 to 600,000. Molecular weight of acrylate polymers can be measured by gel permeation chromatography, which is known to those skilled in the art.

[0050] To control the physical characteristics of the acrylate polymer and the polymerization, it is preferred that monomers of molecular weight of below 500, even more preferably below 200 be used in the polymerization. Further, although optionally larger molecular weight monomers (linear macromonomers such as ELVACITE™ from

[0051] ICI) can be used in the polymerization, it is preferred that they are not used. Thus, preferably no monomer of molecular weight (MW) above 5000, more preferably no monomer of MW above 2000, even more preferably no monomer of MW above 500, is to be included in the polymerization to form the acrylate polymer. Thus, in the present invention, preferably, proadhesive polymers can be formed without macromonomers, or substantially without macromonomers, to have adhesive properties too stiff for PSA as is without incorporation of a large amount of permeation enhancers and drug. However, such proadhesives will become suitable for adhering to the skin as PSA in patch application after the appropriate amount of permeation enhancer and drug are dissolved therein.

[0052] However, if desired, in certain embodiments, optionally, the reservoir can include diluent materials capable of reducing quick tack, increasing viscosity, and/or toughening the reservoir structure, such as polybutylmethacrylate (ELVACITE, manufactured by ICI Acrylics, e.g., ELVACITE 1010, ELVACITE 1020, ELVACITE 20), polyvinylpyrrolidone, high molecular weight acrylates, i.e., acrylates having an average molecular weight of at least 500,000, and the like.

[0053] The acrylate polymers of the present invention can dissolve a large amount of permeation enhancer and allow the resulting drug and permeation enhancer-containing adhesive to have the desired adhesive and cohesive property without the drug or permeation enhancer separating out of the acrylate polymer matrix either as crystals or as oil. The resulting composition will be in the T_g and compliance range that it can be applied to a body surface without leaving an undesirable amount of residue material on the body surface upon removal of the device. The preferred acrylate polymer is not cross-linked. It is contemplated, however, that if desired, a nonsubstantial amount of cross-linking may be done, so long as it does not change substantially the T_g , creep compliance and elastic modulus of the acrylate polymer. It is also found that higher T_g and higher molecular weight of the acrylate are important for the acrylate polymer tolerating high enhancer loading. Since the measurement of the molecular weight of an acrylate polymer is difficult, precise or definite values are often not obtainable. More readily obtainable parameters that are related to molecular weight and drug and enhancer tolerance (i.e., solubility) are creep compliance and elastic modulus.

[0054] Enhancers typically behave as plasticizers to acrylate adhesives. The addition of an enhancer will result in a decrease in modulus as well as an increase in creep compliance, the effect of which is significant at high enhancer loading. A high loading of enhancers will also lower the T_g of the acrylate polymer. Thus, to achieve a proadhesive that is tolerant of high enhancer loading, other than increasing the T_g by using a higher ratio of hard monomer to soft monomer and the selection of suitable monomers, it is desirable to provide suitable higher molecular weight such that chain entanglement would help to achieve the desirable rheology. As a result, selecting a higher T_g and higher molecular weight for a proadhesive will increase the elastic modulus and decrease the creep compliance of the acrylate, making the proadhesive more enhancer tolerant. The measurement of the molecular weight of an acrylate polymer is often method-dependant and is strongly affected by polymer composition, since acrylate polymers discussed here are mostly copolymers, not homopolymers. More readily obtainable parameters that relate to molecular weight and drug and enhancer tolerance (i.e., solubility) are creep compliance and elastic modulus.

[0055] Especially useful polymeric materials for forming drug-containing PSA are acrylate polymers that, before the incorporation of drugs, enhancers, etc., and other ingredients for transdermal formation, have creep compliance (measured at 30°C and 3600 second) of about 7×10^{-5} cm²/dyn or below and storage modulus G' about 8×10^5 dyn/cm² or above. Preferably the creep compliance is about 6×10^{-5} cm²/dyn to 2×10^{-6} cm²/dyn, more preferably about 5×10^{-5} cm²/dyn to 4×10^{-6} cm²/dyn. Preferably the storage modulus is about 8×10^5 dyn/cm² to 5×10^6 dyn/cm², more preferably about 9×10^5 dyn/cm² to 3×10^6 dyn/cm². Such creep compliance and modulus will render these acrylate polymers too stiff and unsuitable "as is" for dermal PSA applications. However, it was found that after formulating into a transdermal system with drugs, permeation enhancers, and the like, which produce plasticizing effect as well as tackifying effect, the acrylate polymers plasticized with permeation enhancers and/or drug would have a desirable storage modulus and creep compliance that are suitable for transdermal PSA applications. For example, the plasticized material would have a resulting creep compliance that is about 1×10^{-3} cm²/dyn or less, preferably more than about 7×10^{-5} cm²/dyn, preferably from about 7×10^{-5} cm²/dyn to 6×10^{-4} cm²/dyn, more preferably about 1×10^{-4} cm²/dyn to 6×10^{-4} cm²/dyn. The preferred storage modulus of the plasticized acrylate polymer is about 1×10^5 dyn/cm² to 8×10^5 dyn/cm², preferably about 1.2×10^5 dyn/cm² to 6×10^5 dyn/cm², more preferably about 1.4×10^5 dyn/cm² to 5×10^5 dyn/cm².

[0056] It was found that incorporating the proper selection of drug and other ingredients (such as permeation enhancers) and using the appropriate amounts thereof can change the T_g , storage modulus G' and creep compliance to result in an effective transdermal drug delivery system with the right adhesive properties for the desirable length of time, such as 24 hours, 3 day, or even 7 day application on a body surface. Such transdermal drug delivery systems will have little or no cold flow. As used herein, "little cold flow" means that any shape change of the device caused by cold flow is not noticeable by an average person on which the device is applied over the time of use. Particularly useful for forming adhesives incorporating an increased amount of beneficial agents (including drugs and permeation enhancers) over prior adhesives in transdermal drug delivery are the acrylic formulations containing a relatively lower percentage of soft

monomers. It has been found that increasing the molecular weight increases the modulus of elasticity and decreases the polymer chain mobility via chain entanglements. Also, increasing hard monomer content increases the glass transition temperature.

[0057] As aforementioned, the reservoir 3 can include a single phase polymeric composition, free of undissolved components, containing an amount of the drug sufficient to induce and maintain the desired therapeutic effect in a human for, e.g., at least three days. The present invention has utility in connection with the delivery of drugs within the broad class normally delivered through body surfaces and membranes, including skin. In general, this includes therapeutic agents in all of the major areas, including, but not limited to, ACE inhibitors, adenohipophoseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics, antipyretics and anti-inflammatory agents, androgens, local and general anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic agents, anticholinesterase agents, anticoagulants, antidiabetic agents, antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents, antiepileptic agents, antiestrogens, antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine agents, antimuscarinic agents, antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet agents, antiprogestins, antischizophrenia agents, antithyroid agents, antitussives, antiviral agents, atypical antidepressants, azaspirodecandiones, barbiturates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts, agents affecting volume and composition of body fluids, butyrophonones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators, contraceptive agents, dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine antagonists, hormones, norelgestromin, 5-hydroxytryptamine antagonists, drugs for the treatment of hyperlipoproteinemia, hypnotics and sedatives, immunosuppressive agents, laxatives, methylxanthines, moncamine oxidase inhibitors, neuromuscular blocking agents, organic nitrates, opioid analgesics and antagonists, pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel blockers, agents for spasticity and acute muscle spasms, succinimides, thioxanthines, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins and the like, alone or in combination. Basic drugs such as opioids (e.g., fentanyl and analogs: alfentanil, carfentanil, lofentanil, remifentanil, sufentanil, trefentanil, and the like), galantamine, and the salts and esters of such basic drugs are well suited to be incorporated in the reservoir with the acrylate polymer.

[0058] The drug can be included in the reservoir at an amount of about 1 to 20 wt%, preferably about 2 to 15 wt%. With the aid of a large quantity of permeation enhancers in a reservoir of the present invention, many drugs can now be delivered through the body surface for therapeutic effect.

[0059] As indicated in the above, in some embodiments, the reservoir or the adhesive may contain additional components such as additives, permeation enhancers, stabilizers, dyes, diluents, plasticizer, tackifying agent, pigments, carriers, inert fillers, antioxidants, excipients, gelling agents, anti-irritants, vasoconstrictors and other materials as are generally known to the transdermal art. Typically, such materials are present below saturation concentration in the reservoir.

[0060] Permeation enhancers can be useful for increasing the skin permeability of the drug or drugs to achieve delivery at therapeutically effective rates. Such permeation enhancers can be applied to the skin by pretreatment or currently with the drug, for example, by incorporation in the reservoir. A permeation enhancer should have the ability to enhance the permeability of the skin for one, or more drugs or other biologically active agents. A useful permeation enhancer would enhance permeability of the desired drug or biologically active agent at a rate adequate to achieve therapeutic plasma concentrations from a reasonably sized patch (e.g., about 5 to 50 cm², although it may be larger). Some useful permeation enhancers include non-ionic surfactants, one or more can be selected from the group including glyceryl mono-oleate, glyceryl monolaurate, sorbitan mono-oleate, glyceryl tri-oleate, and isopropyl myristate. The nonionic surfactant can be used in the amount of about 0.1 to 30 wt % solids to the total composition of the reservoir layer. Examples of permeation enhancers include, but are not limited to, fatty acid esters of fatty acid esters of alcohols, including glycerin, such as capric, caprylic, dodecyl, oleic acids; fatty acid esters of isosorbide, sucrose; polyethylene glycol; caproyl lactic acid; laureth-2; laureth-2 acetate; laureth-2 benzoate; laureth-3 carboxylic acid; laureth-4; laureth-5 carboxylic acid; oleth-2; glyceryl pyroglutamate oleate; glyceryl oleate; N-lauroyl sarcosine; N-myristoyl sarcosine; N-octyl-2-pyrrolidone; lauraminopropionic acid; polypropylene glycol-4-laureth-2; polypropylene glycol-4-laureth-5dimethyl lauramide; lauramide diethanolamine (DEA). Preferred enhancers include, but are not limited to, lauryl pyroglutamate (LP), glyceryl monolaurate (GML), glyceryl monocaprylate, glyceryl monocaprinate, glyceryl monooleate (GMO), oleic acid, N-lauryl sarcosine, ethyl palmitate, laureth-2, laureth-4, and sorbitan monolaurate. Additional examples of suitable permeation enhancers are described, for example, in U.S. Pat. Nos.: 5,785,991; 5,843,468; 5,882,676; and 6,004,578.

[0061] In some embodiments, especially some in which the reservoir does not necessarily have adequate adhesive properties and a separate adhesive layer is used, a dissolution assistant can be incorporated in the reservoir to increase

the concentration of the drug or biologically active ingredient within the reservoir layer. As for the dissolution assistant, one or more can be selected from the group including triacetin, isopropyl alcohol, propylene glycol, dimethylacetamide, propylene carbonate, diethylethanolamine, diethyl amine, triethylamine, N-methyl morpholine, benzalkonium chloride, oleic acid, lactic acid, adipic acid, succinic acid, glutaric acid, sebacic acid, and hydroxycaprylic acid. Permeation enhancers can also act as solubilization assistants.

[0062] As used herein, "permeation enhancers" is meant to include dissolution assistants, unless specified otherwise in context. Permeation enhancers (not including dissolution assistants) can constitute up to about 35% solids by weight, preferably about 0.1 to 30% by weight and more preferably about 1 to 25% by weight in the reservoir in a transdermal drug delivery device of the present invention. As used herein, the term "combination" when refers to selection of two or more chemicals means the chemicals are selected together and not necessarily that they be chemically combined together in a reaction.

[0063] In some embodiments, especially for drugs that do not transdermally permeate readily, a large amount of permeation enhancer may be needed to aid the drug in transdermal delivery. The present invention is especially suitable for such Transdermal delivery systems. In such cases, one or more permeation enhancers, alone or in combination, and which may include dissolution assistants, can constitute about 5 to 40% by weight, preferably about 10 to 35% by weight, and more preferably about 15 to 30% by weight solids of the resulting reservoir that has adequate pressure sensitive adhesive properties.

[0064] In certain embodiments, optionally, certain other plasticizer or tackifying agent is incorporated in the polyacrylate composition to improve the adhesive characteristics. Examples of suitable tackifying agents include, but are not limited to, aliphatic hydrocarbons; aromatic hydrocarbons; hydrogenated esters; polyterpenes; hydrogenated wood resins; tackifying resins such as ESCOREZ, aliphatic hydrocarbon resins made from cationic polymerization of petrochemical feedstocks or the thermal polymerization and subsequent hydrogenation of petrochemical feedstocks, rosin ester tackifiers, and the like; mineral oil and combinations thereof. The tackifying agent employed should be compatible with the polymer or blend of polymers.

[0065] Transdermal delivery patches typically have protective layers. For example, as shown in FIGS. 1 and 2, the patch 1 further includes a peelable protective layer 5. The protective layer 5 is made of a polymeric material that may be optionally metallized. Examples of the polymeric materials include polyurethane, polyvinyl acetate, polyvinylidene chloride, polypropylene, polycarbonate, polystyrene, polyethylene, polyethylene terephthalate, polybutylene terephthalate, paper, and the like, and a combination thereof. In preferred embodiments, the protective layer includes a siliconized polyester sheet.

[0066] A wide variety of materials that can be used for fabricating the various layers of the transdermal delivery patches according to this invention have been described above. It is contemplated that the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions is practicable.

[0067] With patches made with acrylate polymers of the present invention, to assess transdermal flux of a drug from a patch, flux can be measured with a standard procedure using Franz cells or using an array of formulations. Flux experiments are done on isolated human cadaver epidermis. With Franz cells, in each Franz diffusion cell a disc of epidermis is placed on the receptor compartment. A transdermal delivery system is placed over the diffusion area (1.98 cm²) in the center of the receptor. The donor compartment is then added and clamped to the assembly. At time 0, receptor medium solution (between 21 and 24 ml, exactly measured) is added into the receptor compartment and the cell maintained at 35°C. This temperature yields a skin surface temperature of 30-32°C. Samples of the receptor compartment are taken periodically to determine the skin flux and analyzed by HPLC. In testing flux with an array of transdermal miniature patches, formulations are prepared by mixing stock solutions of each of the mixture components of formulation in organic solvents (about 15 wt% solids), followed by a mixing process. The mixtures are then aliquoted onto arrays as 4-mm diameter drops and allowed to dry, leaving-behind solid samples or "dots." (i.e., mini-patches). The miniature patches in the arrays are then tested individually for skin flux using a permeation array, whose principle of drug flux from a formulation patch through epidermis to a compartment of receptor medium is similar to that of Franz cells (an array of miniature cells). The test array has a plurality of cells, a piece of isolated human epidermis large enough to cover the whole array, and a multiple well plate with wells acting as the receptor compartments filled with receptor medium. The assembled permeation arrays are stored at 32 °C and 60 % relative humidity for the duration of the permeation experiments. Receptor fluid is auto-sampled from each of the permeation wells at regular intervals and then measured by HPLC for flux of the drug.

Administration of the Drug

[0068] On application of the transdermal device (patch) to the skin of an individual in need thereof, the drug in the drug reservoir of the transdermal patch diffuses into the skin where it is absorbed into the bloodstream to produce a systemic therapeutic effect. The onset of the therapeutic depends on various factors, such as, potency of the drug, the

solubility and diffusivity of the drug in the skin, thickness of the skin, concentration of the drug within the skin application site, concentration of the drug in the drug reservoir, and the like. Typically, it is preferable that a patient experiences an adequate effect within a few hours (e.g., 3-6 hours) of initial application. However, this is significant only on the initial application. On repeated sequential applications, the residual drug in the application site of the patch is absorbed by the body at approximately the same rate that drug from the new patch is absorbed into the new application area. Thus the patient should not experience any interruption of the therapeutic effect, such as analgesia. When the patch is removed, the therapeutic effect continues until the amount of residual drug in the skin is reduced and the drug cleared from the systemic circulation via various metabolic pathways.

[0069] When continuous therapeutic effect is desired the used patch would be removed and a fresh patch is applied to a new location. For example, the used patch would be sequentially removed and replaced with a fresh patch at the end of the administration period to provide continual therapeutic effect. Since absorption of the drug from the fresh patch into the new application area usually occurs at substantially the same rate as absorption by the body of the residual drug within the previous application site of the patch, blood levels will remain substantially constant.

[0070] Depending on the drug to be delivered, administration of a patch can be maintained for a few days, e.g., at least three days, and up to 7 days, with 3-4 day regimen being considered preferable. In certain preferred embodiments, at least 3%, but not more than 40%, of the total amount of the drug in the patch is administered during approximately the first 24 hours of use; at least 6%, but not more than 50%, of the total amount of the drug is administered during approximately the first 48 hours of use; and at least 10%, but not more than 75%, of the total amount of the drug is administered during the administration period.

Methods of Manufacture

[0071] The transdermal devices are manufactured according to known methodology. For example, in an embodiment, a solution of the polymeric reservoir material, as described above, is added to a double planetary mixer, followed by addition of desired amounts of the drug, permeation enhancers, and other ingredients that may be needed. Preferably, the polymeric reservoir material is an acrylate material. The acrylate material is solubilized in an organic solvent, e.g., ethanol, ethyl acetate, hexane, and the like. The mixer is then closed and activated for a period of time to achieve acceptable uniformity of the ingredients. The mixer is attached by means of connectors to a suitable casting die located at one end of a casting/film drying line. The mixer is pressurized using nitrogen to feed solution to the casting die. Solution is cast as a wet film onto a moving siliconized polyester web. The web is drawn through the lines and a series of ovens are used to evaporate the casting solvent to acceptable residual limits. The dried reservoir film is then laminated to a selected backing membrane and the laminate is wound onto the take-up rolls. In subsequent operations, individual transdermal patches are die-cut, separated and unit-packaged using suitable pouchstock. Patches are placed in cartons using conventional equipment. In another process, the drug reservoir can be formed using dry-blending and thermal film-forming using equipment known in the art. Preferably, the materials are dry blended and extruded using a slot die followed by calendering to an appropriate thickness.

EXAMPLES

[0072] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only. In the following examples all percentages are by weight unless noted otherwise. T_g was determined by DSC (Differential Scanning Calorimetry) with 10°C/min heating rate. Modulus G' is storage modulus at 25°C and 1 rad/s frequency (Frequency sweep experiment was conducted using AR-2000 rheometer from TA Instruments (TA Instruments, 109 Lukens Drive, New Castle, DE 19720). The test conditions were: strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, gap around 1000 micron). Creep compliance tests were conducted using AR-2000 rheometer from TA Instruments. The test conditions were: stress 1000 dyn/cm², temperature 30°C, time 3600 seconds, gap around 1000 microns. One skilled in the art will know how to measure T_g , creep compliance, and storage modulus in view of the present disclosure.

[0073] Transdermal flux can be measured with a standard procedure using Franz cells or using an array of formulations. Flux experiments were done on isolated human cadaver epidermis. With Franz cells, in each Franz diffusion cell a disc of epidermis is placed on the receptor compartment. A transdermal delivery system is placed over the diffusion area (1.98 cm²) in the center of the receptor. The donor compartment is then added and clamped to the assembly. At time 0, receptor medium solution (between 21 and 24 ml, exactly measured) is added into the receptor compartment and the cell maintained at 35°C. This temperature yields a skin surface temperature of 30-32°C. Samples of the receptor compartment are taken periodically to determine the skin flux and analyzed by HPLC. In testing flux with an array of transdermal miniature patches, formulations are prepared by mixing stock solutions of each of the mixture components of formulation in organic solvents (about 15wt% solids), followed by a mixing process. The mixtures are then aliquoted onto arrays as 4-mm diameter drops and allowed to dry, leaving behind solid samples or "dots." (i.e., mini-patches). The miniature

patches in the arrays are then tested individually for skin flux using a permeation array, whose principle of drug flux from a formulation patch through epidermis to a compartment of receptor medium is similar to that of Franz cells (an array of miniature cells). The test array has a plurality of cells, a piece of isolated human epidermis large enough to cover the whole array, and a multiple well plate with wells acting as the receptor compartments filled with receptor medium. The assembled permeation arrays are stored at 32 °C and 60 % relative humidity for the duration of the permeation experiments. Receptor fluid is auto-sampled from each of the permeation wells at regular intervals and then measured by HPLC for flux of the drug.

EXAMPLE 1

[0074] A monomer mix containing butyl acrylate, 2-hydroxyethyl acrylate, t-octyl acrylamide, acrylic acid, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The ratios of the monomers and initiator added totally, i.e., butyl acrylate: 2-hydroxyethyl acrylate: t-octyl acrylamide: acrylic acid: AIBN were 59: 25.5: 9.5: 6: 2. The material was then held at reflux for a suitable period of time. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around $9 \times 10^5 \text{ dyn/cm}^2$, creep compliance of around $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$, and glass transition temperature of -8 °C, and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

COMPARATIVE EXAMPLE 2

[0075] A monomer mix containing butyl acrylate, 2-hydroxypropyl acrylate, t-octyl acrylamide, acrylic acid, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The material was held at reflux for a suitable period of time. The ratios of the monomers and initiator added totally, i.e., butyl acrylate: 2-hydroxypropyl acrylate: t-octyl acrylamide: acrylic acid: AIBN were 59: 25.5: 9.5: 6: 2. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around $8 \times 10^5 \text{ dyn/cm}^2$, creep compliance of around $4 \times 10^{-5} \text{ cm}^2/\text{dyn}$, and glass transition temperature of -8 °C, and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

EXAMPLE 3

[0076] A monomer mix containing vinyl acetate, 2-hydroxyethyl acrylate, 2-ethylhexyl acrylate, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The material was held at reflux for a suitable period of time. The ratios of the monomers and initiator added totally, i.e., vinyl acetate: 2-hydroxyethyl acrylate: 2-ethylhexyl acrylate: AIBN were 50: 10: 40: 1.2. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around $2 \times 10^6 \text{ dyn/cm}^2$, creep compliance of around $4 \times 10^{-6} \text{ cm}^2/\text{dyn}$, and glass transition temperature of -14 °C, and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

EXAMPLE 4

[0077] A monomer mix containing vinyl acetate, 2-hydroxyethyl acrylate, 2-ethylhexyl acrylate, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The ratios of the monomers and initiator added totally, i.e., vinyl acetate: 2-hydroxyethyl acrylate: 2-ethylhexyl acrylate: AIBN were 60: 20: 20: 1.2. The material was held at reflux for a suitable period of time. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around $4 \times 10^6 \text{ dyn/cm}^2$, creep compliance of around $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$, and glass transition temperature of -8 °C, and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

EXAMPLE 5

[0078] Polyacrylate adhesive DURO-TAK® 87-2287, (from National Starch & Chemical Co.) and proadhesives from EXAMPLE 3 and EXAMPLE 4 were analyzed with and without permeation enhancers. The data in Table 1 clearly

demonstrate the effect of enhancer on the properties of current commercial acrylic adhesive as well as the novel polyacrylate compositions described in this application. DURO-TAK® 87-2287 adhesive with a T_g of -34°C had severe cold flow at 20% lauryl lactate loading level. (The monomeric components of DURO-TAK® 87-2287 are mostly vinyl acetate, 2-ethylhexyl acrylate, and hydroxyethyl acrylate.) Such cold flow phenomenon is the reason this adhesive and most similar commercial pressure sensitive adhesive systems are not suitable for applications where relatively high loadings of enhancers are needed. LL is enhancer lauryl lactate. DURO-TAK® 87-2287 had unacceptable rheological properties (severe cold flow) for transdermal application in the presence of 20% lauryl lactate. (Based on this invention, it was also found that many other PSA's with T_g , creep compliance and storage modulus similar to DURO-TAK® 87-2287 in the range suitable for PSA as is would behave similarly). The data in Table 1 demonstrated that the current commercial acrylate PSA were not suitable for applications where high loading of enhancers is needed. It was found that transdermal patches started to have undesirable rheological properties, such as the tendency to cold flow and low cohesive strength, when creep compliance is larger than $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$. It has been found that typically for the prior commercial transdermal PSAs, enhancer loading is usually less than 20% due to the impact of enhancer on PSA rheological properties.

[0079] The improvement of enhancer tolerance using the novel polyacrylate composition described in this application can also be seen from the data in Table 1. By increasing the ratio of hard to soft monomer in the formulations, the glass transition temperatures were increased. The molecular weight was also increased. As a result, the polyacrylate compositions described in EXAMPLES 3 and 4 had higher modulus and lower creep compliance as can be seen from the data in Table 1. This resulted in polyacrylate compositions not suitable for pressure sensitive adhesive application in pure form due to high modulus. However, these polyacrylate compositions had better enhancer tolerance. As a result, the compositions after the addition of 35 wt% LL had the desired rheological properties for transdermal application. As can be seen from the data in Table 1, desirable creep compliance was still present when enhancer loading was 35 wt%.

[0080] Further, the data in Table 2 showed that when compared to another currently available commercial pressure sensitive adhesive DURO-TAK® 87-4287, the polyacrylate from Example 3 provides better enhancer tolerance.

Table 1. Effect of enhancer lauryl lactate (LL) on adhesive properties.

Sample	T_g , $^\circ\text{C}$	Modulus G' , dyn/cm^2	Creep compliance, cm^2/dyn
DURO-TAK® 87-2287	-34	2.1×10^5	1.3×10^{-4}
Polyacrylate composition from EXAMPLE 3	-14	2.0×10^6	4.0×10^{-6}
Polyacrylate composition from EXAMPLE 4	-8	4.0×10^6	2.0×10^{-6}
20wt% LL in DURO-TAK® 87-2287	---	5.6×10^4	1.84×10^{-3}
34wt% LL in Polyacrylate composition from EXAMPLE 3	---	1.0×10^5	3.2×10^{-4}
35wt% LL in Polyacrylate composition from EXAMPLE 4	---	1.2×10^5	4.0×10^{-4}

Table 2. Effect of enhancer oleic acid (OA) on adhesive properties.

Sample	T_g , $^\circ\text{C}$	Modulus G' , dyn/cm^2	Creep compliance, cm^2/dyn
DURO-TAK® 87-4287	-34	3.4×10^5	4.3×10^{-5}
Polyacrylate composition from EXAMPLE 3	-14	2.0×10^6	4.0×10^{-6}
25wt% OA in DURO-TAK® 87-4287	---	4.9×10^4	9.1×10^{-4}
35wt% OA in Polyacrylate composition from EXAMPLE 3	---	6.1×10^4	2.0×10^{-4}

[0081] Specific examples of various transdermal patches of the invention that are capable of administering drugs for extended periods of time will be described in the examples below. The adhesive-reservoir patches in which the reservoir includes a single phase polymeric composition of free undissolved components containing an therapeutically effective amount of drug at subsaturation concentration are preferred.

EXAMPLE 6

[0082] A transdermal patch containing active substance galantamine were prepared as follows:

91.6 g polyacrylate solution (a 34.53 wt% solution of the polyacrylate described in EXAMPLE 1), 13.5 g galantamine, 3.0 g lauric acid, 2.3 g lauryl pyrrolidone, and 4.6 g oleic acid were mixed and homogenized. The solution was spread at a thickness of 12-15 mil (0.3-0.375 mm) on a siliconized PET film that is about 2-3 mil (0.05-0.075 mm) thick. The mass was dried at 65 °C over a period of 90 minutes. After solvent evaporation, a 2-3 mil (0.05-0.075 mm) thick PET backing layer was laminated on to the adhesive drug reservoir layer using standard procedures. Individual patches with different size were die-cut from this laminate. It was found that the polyacrylate adhesive in the resulting patch had desirable storage modulus of around 2.1×10^5 dyn/cm², and desirable creep compliance of around 4.1×10^{-4} cm²/dyn. Comparatively, the polyacrylate without the drug and the enhancers had glass transition temperature of -8°C, storage modulus of around 9×10^5 dyn/cm², and creep compliance of around 7×10^{-5} cm²/dyn, and was too stiff and had inadequate adhesive properties. It was found that the patches could deliver galantamine through cadaver skin in a Franz cell at a flux rate of 8.9 µg/cm².hr. This shows such polyacrylate can be made into patches for galantamine therapy, e.g., for dementia, Alzheimer disease, etc.

COMPARATIVE EXAMPLE 7

[0083] A 99.8g polyacrylate solution (about 36.92 wt% of polyacrylate described in COMPARATIVE EXAMPLE 2), 15.6 g galantamine, 12.1 g oleic acid, and 1.0 lauric acid were mixed and homogenized. The resulting solution was spread at a thickness of 10-12 mil on a silicone-coated PET film about 2-3 mil (0.05-0.075 mm) thick. The mass was dried at 65 °C over a period of 90 minutes. After solvent evaporation, a 2-3 mil (0.05-0.075 mm) thick PET backing layer was laminated on to the adhesive drug reservoir layer using standard procedures. Individual patches with different size were die-cut from this laminated. It was found that the polyacrylate adhesive in the resulting patch had desirable storage modulus of around 3.2×10^5 dyn/cm², and desirable creep compliance of around 2.2×10^{-4} cm²/dyn. Comparatively, the polyacrylate without the drug and the enhancers had glass transition temperature of -8 °C, storage modulus of around 9×10^5 dyn/cm² and creep compliance of around 7×10^{-5} cm²/dyn, and was too stiff and had inadequate adhesive properties. It was found that the patches can deliver galantamine through cadaver skin in a Franz cell at a flux rate of 10.9 µg/cm².hr. This shows such polyacrylate can be made into patches for galantamine therapy, e.g., for dementia, Alzheimer disease, etc.

EXAMPLE 8

[0084] A transdermal patch containing active substance norelgestromin were prepared as follows:

A 100.0 g polyacrylate solution (about 42.9 wt% of polyacrylate described in EXAMPLE 3), 3.6 g norelgestromin, 7.8 g GMO, and 1.7 g NLS were mixed and homogenized. The resulting solution was spread at a thickness of 10-12 mil on a silicone-coated PET film of about 2-3 mil (0.05-0.075 mm) thickness. The mass was dried at 65 °C over a period of 90 minutes. After solvent evaporation, a 2-3 mil (0.05-0.075 mm) thick PET backing layer was laminated on to the adhesive drug reservoir layer using standard procedures. Individual patches with different size were die-cut from this laminate. It was found that the polyacrylate adhesive in the resulting patch had desirable storage modulus of around 3.1×10^5 dyn/cm² and desirable creep compliance of around 6.2×10^{-5} cm²/dyn. Comparatively, the polyacrylate without the drug and the enhancers had a storage modulus of around 4×10^6 dyn/cm² and a creep compliance of around 2×10^{-6} cm²/dyn and was too stiff and had inadequate adhesive properties. Further, it has been shown that the polyacrylate of EXAMPLE 3 after incorporating a large amount of permeation enhancer into a single phase (see Table 1), although without the drug, had adequate PSA properties. It was found that the patches were able to deliver norelgestromin through cadaver skin in a Franz cell at a flux rate of 0.4 µg/cm².hr. This shows such polyacrylate can be made into patches for norelgestromin therapy, e.g., for hormone replacement, birth control, etc.

COMPARATIVE EXAMPLE 9

[0085] Nicotine hexanoate (200 grams) is added to 10 Kg of a solution of the polyacrylate of Example 2 (from National Starch & Chemicals, Bridgewater, NJ) in a blended solvent mixture of isopropyl alcohol (13wt%) and 87wt% ethyl acetate to result in a 20wt% solids in solvent(s) solution. This polyacrylate is a polar copolymer and consisted of 26 wt% hydroxyl monomer, 6 wt% monomer with carboxylic acid groups, t-octyl acrylamide, and butyl acrylate. The solution is mixed well and was transferred to a pressurized casting vessel. This solution is fed to a casting head set up to lay down a 0.25 mm

wet thickness film onto a moving web of siliconized polyester, 0.075 mm thick. The film is moved at a rate of about 5 feet per minute through a series of three ovens 30 feet long. The ovens are set at 45 degrees °C, 85 °C and 95 °C, with a total residence time of six minutes. After exiting the ovens, the films would contain typically less than 500 ppm of residual solvent(s). After exiting the ovens, a transdermal backing is laminated to the reverse side of the polyacrylate adhesive. The backing was a 0.05 mm thick layer of linear low density polyethylene. Individual systems of about 3 cm² are cut and the flux of which is tested. It is expected that they have acceptable flux and that such polyacrylate can be made into patches for nicotine therapy, e.g., for smoking cessation.

[0086] The practice of the present invention will employ, unless otherwise indicated, conventional methods used by those in pharmaceutical product development within those of skill of the art.

Claims

1. A device for transdermal administration of drug to an individual through a body surface, comprising: a reservoir including at least one drug, permeation enhancer and an acrylate polymer, wherein the reservoir is of a composition having a creep compliance of 7×10^{-5} cm²/dyn to 2×10^{-6} cm²/dyn if the reservoir were without drug and without permeation enhancer, such that the acrylate polymer has a soft monomer component of no more than 60 wt%, the soft monomer component consisting of monomers having a homopolymer T_g of -80°C to -10°C, the acrylate polymer having 40 wt% or more of a hard monomer component at least a portion of which is hard polar functional monomer, the hard monomer component consisting of monomers having a homopolymer T_g of 0°C to 250°C, the polar functional monomer consisting of monomers that contain hydrogen bonding functional groups selected from hydroxyl, carboxyl and amino groups wherein the hard monomer component is selected from at least one of hydroxyethyl acrylate, acrylic acid, vinyl acetate, and t-octylacrylamide, and the acrylate polymer has 10 to 40 wt% polar functional monomer component at least a portion of which is hard polar functional monomer, the acrylate polymer constituting 45 - 80 wt% of the reservoir and capable of holding the drug and permeation enhancer combination at a dissolved amount of at least 30 wt%, and having a T_g of greater than -15°C if without permeation enhancer and without drug, the reservoir being applicable as a pressure-sensitive-adhesive to the body surface for transdermal delivery, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate and the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm.
2. The device of claim 1 wherein the acrylate polymer includes at least one of a polar functional monomer with hydroxyl group and a polar functional monomer with carboxylic acid group.
3. The device of claim 1 wherein the acrylate polymer includes an acrylic copolymer resulting from (i) 40 to 50 wt% of soft alkyl acrylate monomer component, in which each soft alkyl acrylate monomer having a homopolymer T_g of -80 to -20°C and (ii) 40 to 60 wt% of hard monomer component that is not also a polar functional monomer component, in which each hard monomer having a homopolymer T_g of 0 to 250°C, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
4. The device of claim 3 wherein soft alkyl acrylate monomer component is an alkyl acrylate monomer having 4 to 10 carbon atoms in the alkyl group.
5. The device of claim 1 wherein the acrylate polymer includes 40 to 50 wt% of soft alkyl acrylate monomer component having a homopolymer T_g of less than -20°C, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
6. The device of claim 1 wherein the acrylate polymer includes 40 to 50 wt% of soft alkyl acrylate monomer component having a homopolymer T_g of less than -20°C, hard monomer component having a homopolymer T_g of higher than 20°C, and polar functional monomer having an acidic group, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
7. The device of claim 1 wherein the permeation enhancer and the drug are dissolved in the acrylate polymer and the acrylate polymer has a T_g of 0 to -15°C, if without the dissolved drug and permeation enhancer, whereas the reservoir with the dissolved drug and permeation enhancer has a creep compliance of less than 1×10^{-3} cm²/dyn and storage modulus of 1×10^5 dyn/cm² to 8×10^5 dyn/cm², wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate, the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm, and the stated storage modulus values are as

measured at strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, and gap 1000 μm.

8. The device of claim 1 wherein the acrylate polymer includes a hard modifying monomer component having a homopolymer T_g of 40 to 100°C, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
9. The device of claim 1 wherein the acrylate polymer has an acidic group and hydroxyl group therein and includes 5 to 15 wt% non-functional hard monomer component.
10. The device of claim 1 wherein the acrylate polymer has monomer components consisted essentially of 50 to 60 wt% vinyl acetate, 10-20 wt% hydroxyethyl acrylate, and 20-40 wt% 2-ethylhexyl acrylate.
11. The device of claim 1 wherein the acrylate polymer includes a polar functional monomer selected from the group consisting of acrylic acid, hydroxyethyl acrylate, and hydroxypropyl acrylate.
12. The device of claim 1 wherein the permeation enhancer and the drug are dissolved in the acrylate polymer and the acrylate polymer has a T_g of 0 to -15°C, if without the dissolved drug and permeation enhancer, whereas the acrylate polymer with the drug and permeation enhancer dissolved therein the acrylate polymer forms a reservoir with a T_g of -10 to -20 °C, a creep compliance of less than $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$ and storage modulus of $1 \times 10^5 \text{ dyn/cm}^2$ to $8 \times 10^5 \text{ dyn/cm}^2$, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate, the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm, and the stated storage modulus values are as measured at strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, and gap 1000 μm.
13. The device of claim 1 wherein the acrylate polymer has a T_g of 0 to -15°C if without drug and permeation enhancer, whereas the acrylate polymer having drug and permeation enhancer at above 30 wt% in a single phase forms a reservoir with a T_g of -10 to -20°C, a creep compliance of $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ to $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ and storage modulus of $1 \times 10^5 \text{ dyn/cm}^2$ to $8 \times 10^5 \text{ dyn/cm}^2$, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate, the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm, and the stated storage modulus values are as measured at strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, and gap 1000 μm.
14. The device of claim 1 wherein the acrylate polymer has a T_g of 0 to -15°C, storage modulus of $8 \times 10^5 \text{ dyn/cm}^2$ or above if without drug and permeation enhancer, whereas the acrylate polymer with drug and permeation enhancer at above 30 wt% dissolved therein forms a reservoir with a T_g of -10 to -40°C, a creep compliance of $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ to $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ and storage modulus of $1 \times 10^5 \text{ dyn/cm}^2$ to $8 \times 10^5 \text{ dyn/cm}^2$, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate, the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm, and the stated storage modulus values are as measured at strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, and gap 1000 μm.
15. The device of claim 1 comprising a drug selected from the group consisting of fentanyl, fentanyl analog, galantamine, and norelgestromin.
16. A method of making a reservoir for transdermal drug delivery, comprising: providing an acrylate polymer having a creep compliance of $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$ to $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$ without drug and without permeation enhancer, such that the acrylate polymer has a soft monomer component of no more than 60 wt%, wherein the soft monomer component consists of monomers having a homopolymer T_g of -80° C to -10° C, the acrylate polymer having a hard monomer component of 40 wt% or more, the acrylate polymer hard monomer component consisting of monomers having a homopolymer T_g of 0 ° C to 250 °C, wherein at least a portion of the hard monomer is a hard polar functional monomer, wherein the polar functional monomer consists of monomers that contain hydrogen bonding functional groups selected from hydroxyl, carboxyl and amino groups, wherein the hard monomer component is selected from at least one of hydroxyethyl acrylate, acrylic acid, vinyl acetate, and t-octylacrylamide, the acrylate polymer capable of holding a drug and permeation enhancer combination in the acrylate polymer at a dissolved amount of at least 30 wt%, incorporating the drug and permeation enhancer in the acrylate polymer to result in a single phase reservoir so that dissolved drug and permeation enhancer constitute together more than 20 wt%, and the acrylate polymer constituting 45 wt% to 80 wt% in solids of the reservoir, wherein the reservoir is applicable as a pressure sensitive adhesive to the body surface, wherein the stated T_g values are as measured by differential scanning calorimetry

(DSC) with 10°C/min heating rate and the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm.

17. The method of claim 16 wherein the reservoir with the dissolved drug and permeation enhancer has a glass transition temperature T_g of less than -10 °C whereas the acrylate polymer without drug and without permeation enhancer has a T_g of greater than -15 °C, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
18. The method of claim 16 wherein the acrylate polymer includes (i) 40 to 50 wt% of soft alkyl acrylate monomer component, in which each soft alkyl acrylate monomer therein having a homopolymer T_g of -80 to -20 °C, (ii) 40 to 60 wt% of hard monomer component that is not also a polar functional monomer component, in which each hard monomer component having a homopolymer T_g of 0 to 250 °C, and (iii) 10 to 40 wt% of polar functional monomer component, wherein the soft monomer is an alkyl acrylate monomer having 4 to 10 carbon atoms in the alkyl group, wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate.
19. The method of claim 16 wherein the acrylate polymer has a T_g of 0 to -15 °C if without drug and permeation enhancer, and the reservoir with the dissolved drug and permeation enhancer has a T_g of -10 to -20 °C, a creep compliance of 1×10^{-4} cm²/dyn to 6×10^{-4} cm²/dyn and storage modulus of 1×10^5 dyn/cm² to 8×10^5 dyn/cm², wherein the stated T_g values are as measured by differential scanning calorimetry (DSC) with 10°C/min heating rate, the stated creep compliance values are as measured at stress 1000 dyn/cm², temperature 30°C for 3,600 seconds and gap 1000 μm, and the stated storage modulus values are as measured at strain 1%, temperature 25°C, frequency range 0.1 to 100 rad/s, and gap 1000 μm.

Patentansprüche

1. Eine Methode zur transdermalen Verabreichung eines Medikaments an eine Person durch eine Körperoberfläche bestehend aus: einem Reservoir mit zumindest einem Medikament, einem Permeationsverbesserer und einem Acrylatpolymer, wobei das Reservoir eine Zusammensetzung mit einer Kriech-Compliance von 7×10^{-5} cm²/dyn bis 2×10^{-6} cm²/dyn aufweist, wenn das Reservoir kein Medikament und keinen Permeationsverbesserer enthält, so dass das Acrylatpolymer eine weiche Monomerkomponente von nicht mehr als 60 Gewichts-% aufweist, wobei die weiche Monomerkomponente sich aus Monomeren zusammensetzt, die eine Homopolymer- T_g von -80°C bis -10°C aufweisen, das Acrylatpolymer 40 Gewichts-% oder mehr an einer harten Monomerkomponente aufweist, von der zumindest ein Teil ein hartes, polares, funktionelles Polymer ist, wobei die harte Monomerkomponente aus Monomeren besteht, die eine Homopolymer- T_g von 0°C bis 250°C haben, wobei das polare, funktionelle Monomer aus Monomeren besteht, die wasserstoffbindende, funktionelle Gruppen enthalten, die aus Hydroxyl-, Carboxyl- und Aminogruppen ausgewählt werden, wobei die harte Monomerkomponente aus zumindest einem der Folgenden ausgewählt wird, nämlich Hydroxyethylacrylat, Acrylsäure, Vinylacetat und t-Octylacrylamid, und das Acrylatpolymer 10 bis 40 Gewichts-% an polarer, funktioneller, Monomerkomponente aufweist, wobei zumindest ein Teil hartes, polares, funktionelles Monomer ist, wobei das Acrylatpolymer 45 - 80 Gewichts-% des Reservoirs ausmacht und fähig ist, die Medikament- und Permeationsverbessererkombination in einer aufgelösten Menge von zumindest 30 Gewichts-% zu enthalten, und eine T_g von über -15°C hat, wenn es keinen Permeationsverbesserer und kein Medikament enthält; wobei das Reservoir als druckempfindlicher Haftstoff auf der Körperfläche zwecks transdermalen Verabreichung angewandt werden kann, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden, und die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von 1000 dyn/cm², einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von 1000 μm gemessen werden.
2. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer zumindest entweder einen polaren, funktionellen Monomer mit einer Hydroxylgruppe oder einen polaren, funktionellen Monomer mit einer Carboxylsäuregruppe enthält.
3. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer ein Acrylcopolymer enthält, das sich durch (i) 40 bis 50 Gewichts-% an weicher Alkylacrylatmonomerkomponente ergibt, wobei jedes weiche Alkylacrylatmonomer eine Homopolymer- T_g von -80 bis -20°C aufweist, und (ii) 40 bis 60 Gewichts-% an harter Monomerkomponente enthält, die nicht auch eine polare, funktionelle Monomerkomponente ist, wobei jedes harte Monomer eine Homopolymer- T_g von 0 bis 250°C hat, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden.

4. Die Methode entsprechend Anspruch 3, wobei die weiche Alkylacrylatmonomerkomponente ein Alkylacrylatmonomer mit 4 bis 10 Kohlenstoffatomen in der Alkylgruppe ist.
5. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer 40 bis 50 Gewichts-% an weicher Alkylacrylatmonomerkomponente mit einer Homopolymer- T_g von weniger als -20°C enthält, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden.
6. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer 40 bis 50 Gewichts-% an weicher Alkylacrylatmonomerkomponente mit einer Homopolymer- T_g von weniger als -20°C enthält, die harte Monomerkomponente einer Homopolymer- T_g von mehr als 20°C und ein polares, funktionelles Monomer mit einer Säuregruppe enthält, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden.
7. Die Methode entsprechend Anspruch 1, wobei der Permeationsverbesserer und das Medikament im Acrylatpolymer aufgelöst werden und das Acrylatpolymer eine T_g von 0 bis -15°C hat, wenn kein aufgelöstes Medikament und Permeationsverbesserer vorhanden sind, während das Reservoir mit aufgelöstem Medikament und Permeationsverbesserer eine Kriech-Compliance von unter $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$ und ein Speichermodul von $1 \times 10^5 \text{ dyn}/\text{cm}^2$ bis $8 \times 10^5 \text{ dyn}/\text{cm}^2$ aufweist, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden, wobei die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von $1000 \text{ dyn}/\text{cm}^2$, einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von $1000 \mu\text{m}$ gemessen werden, und die genannten Speichermodulwerte denen entsprechen, die bei Belastung von 1%, einer Temperatur von 25°C , einem Frequenzbereich von 0,1 bis 100 rad/s und einem Abstand von $1000 \mu\text{m}$ gemessen werden.
8. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer eine harte, modifizierende Monomerkomponente enthält, die eine Homopolymer- T_g von 40 bis 100°C hat, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden.
9. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer eine Säuregruppe und eine Hydroxylgruppe enthält und 5 bis 15 Gewichts-% einer nichtfunktionellen, harten Monomerkomponente enthält.
10. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer Monomerkomponenten aufweist, die im Wesentlichen aus 50 bis 60 Gewichts-% Vinylacetat, 10-20 Gewichts-% Hydroxyethylacrylat und 20-40 Gewichts-% 2-Ethylhexylacrylat bestehen.
11. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer ein polares, funktionelles Monomer enthält, das aus der Gruppe bestehend aus Acrylsäure, Hydroxyethylacrylat und Hydroxypropylacrylat ausgewählt wird.
12. Die Methode entsprechend Anspruch 1, wobei der Permeationsverbesserer und das Medikament im Acrylatpolymer aufgelöst werden und das Acrylatpolymer eine T_g von 0 bis -15°C hat, wenn kein aufgelöstes Medikament und Permeationsverbesserer vorhanden sind, während das Acrylatpolymer mit darin aufgelöstem Medikament und Permeationsverbesserer ein Reservoir mit einer T_g von -10 bis -20°C bildet, eine Kriech-Compliance von unter $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$ und ein Speichermodul von $1 \times 10^5 \text{ dyn}/\text{cm}^2$ bis $8 \times 10^5 \text{ dyn}/\text{cm}^2$ aufweist, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden, wobei die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von $1000 \text{ dyn}/\text{cm}^2$, einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von $1000 \mu\text{m}$ gemessen werden, und die genannten Speichermodulwerte denen entsprechen, die bei Belastung von 1 %, einer Temperatur von 25°C , einem Frequenzbereich von 0,1 bis 100 rad/s und einem Abstand von $1000 \mu\text{m}$ gemessen werden.
13. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer eine T_g von 0 bis -15°C aufweist, wenn kein Medikament und Permeationsverbesserer vorhanden sind, während das Acrylatpolymer mit Medikament und Permeationsverbesserer von mehr als 30 Gewichts-% in einer einzelnen Phase ein Reservoir mit einer T_g von -10 bis -20°C , einer Kriech-Compliance von unter $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ bis $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ und ein Speichermodul von $1 \times 10^5 \text{ dyn}/\text{cm}^2$ bis $8 \times 10^5 \text{ dyn}/\text{cm}^2$ bildet, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von $10^\circ\text{C}/\text{Min.}$ gemessen werden, wobei die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von $1000 \text{ dyn}/\text{cm}^2$, einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von $1000 \mu\text{m}$ gemessen werden, und die genannten Speichermodulwerte denen

entsprechen, die bei Belastung von 1 %, einer Temperatur von 25°C, einem Frequenzbereich von 0,1 bis 100 rad/s und einem Abstand von 1000 μm gemessen werden.

14. Die Methode entsprechend Anspruch 1, wobei das Acrylatpolymer eine T_g von 0 bis -15°C und ein Speichermodul von $8 \times 10^5 \text{ dyn/cm}^2$ oder darüber aufweist, wenn kein Medikament und Permeationsverbesserer vorhanden sind, während das Acrylatpolymer mit darin aufgelöstem Medikament und Permeationsverbesserer von mehr als 30 Gewichts-% ein Reservoir mit einer T_g von -10 bis -40°C, einer Kriech-Compliance von $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ bis $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ und einem Speichermodul von $1 \times 10^5 \text{ dyn/cm}^2$ bis $8 \times 10^5 \text{ dyn/cm}^2$ bildet, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden, wobei die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von 1000 dyn/cm^2 , einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von 1000 μm gemessen werden, und die genannten Speichermodulwerte denen entsprechen, die bei Belastung von 1 %, einer Temperatur von 25°C, einem Frequenzbereich von 0,1 bis 100 rad/s und einem Abstand von 1000 μm gemessen werden.
15. Die Methode entsprechend Anspruch 1, die ein Medikament enthält, das aus der Gruppe bestehend aus Fentanyl, Fentanylanalogue, Galantamin und Norelgestromin ausgewählt wird.
16. Ein Verfahren zur Herstellung eines Reservoirs zur transdermalen Medikamentenabgabe bestehend aus: der Bereitstellung eines Acrylatpolymers mit einer Kriech-Compliance von $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$ bis $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$ ohne Medikament und Permeationsverbesserer, so dass das Acrylatpolymer eine weiche Monomerkomponente von nicht mehr als 60 Gewichts-% aufweist, wobei die weiche Monomerkomponente sich aus Monomeren zusammensetzt, die eine Homopolymer- T_g von -80°C bis -10°C aufweisen, das Acrylatpolymer 40 Gewichts-% oder mehr an einer harten Monomerkomponente aufweist, wobei die harte Acrylatmonomerkomponente eine Homopolymer- T_g von 0°C bis 250°C hat, wobei zumindest ein Teil des harten Monomers hartes, polares, funktionelles Monomer ist, wobei das polare, funktionelle Monomer aus Monomeren besteht, die wasserstoffbindende, funktionelle Gruppen enthalten, die aus Hydroxyl-, Carboxyl- und Aminogruppen ausgewählt werden, wobei die harte Monomerkomponente aus zumindest einem der Folgenden ausgewählt wird, nämlich Hydroxyethylacrylat, Acrylsäure, Vinylacetat und t-Octylacrylamid, und das Acrylatpolymer fähig ist, die Medikament- und Permeationsverbessererkombination in einer aufgelösten Menge von zumindest 30 Gewichts-% zu enthalten, wobei das Medikament und der Permeationsverbesserer im Acrylatpolymer inkorporiert sind, um ein Einzelphasenreservoir zu bilden, so dass das aufgelöste Medikament und Permeationsverbesserer zusammen mehr als 20% Gewichts-% ausmachen, und das Acrylatpolymer mehr als 45 Gewichts-% bis 80 Gewichts-% des Feststoffs des Reservoirs ausmacht, wobei das Reservoir als druckempfindlicher Haftstoff auf der Körperfläche angewandt werden kann, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden, und die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von 1000 dyn/cm^2 , einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von 1000 μm gemessen werden.
17. Das Verfahren entsprechend Anspruch 16, wobei das Reservoir mit dem aufgelösten Medikament und Permeationsverbesserer eine Glasübergangstemperatur T_g von unter -10°C aufweist, während das Acrylatpolymer ohne Medikament und Permeationsverbesserer eine T_g von über -15°C aufweist, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden.
18. Das Verfahren entsprechend Anspruch 16, wobei das Acrylatpolymer Folgendes umfasst; (i) 40 bis 50 Gewichts-% einer weichen Alkylacrylatmonomerkomponente, bei der jedes darin enthaltene weiche Alkylacrylatmonomer eine Homopolymer- T_g von -80 bis -20°C aufweist; (ii) 40 bis 60 Gewichts-% einer harten Monomerkomponente, die nicht auch eine polare, funktionelle Monomerkomponente ist, wobei jedes harte Monomer eine Homopolymer- T_g von 0 bis 250°C hat, und (iii) 10 bis 40 Gewichts-% einer polaren, funktionellen Monomerkomponente, wobei das weiche Monomer ein Alkylacrylatmonomer mit 4 bis 10 Kohlenstoffatomen in der Alkylgruppe ist, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden.
19. Das Verfahren entsprechend Anspruch 16, , wobei das Acrylatpolymer eine T_g von 0 bis -15°C, aufweist, wenn kein Medikament und Permeationsverbesserer vorhanden sind, und das Reservoir mit dem aufgelösten eine T_g von -10 bis -20°C, eine Kriech-Compliance von $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ bis $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ und ein Speichermodul von $1 \times 10^5 \text{ dyn/cm}^2$ bis $8 \times 10^5 \text{ dyn/cm}^2$ aufweist, wobei die genannten T_g -Werte denen entsprechen, die durch Differenzthermoanalyse (DSC) bei einer Erwärmungsrate von 10°C/Min. gemessen werden, wobei die genannten Kriech-Compliance-Werte denen entsprechen, die bei Stress von 1000 dyn/cm^2 , einer Temperatur von 30°C für 3.600 Sekunden und einem Abstand von 1000 μm gemessen werden, und die genannten Speichermodulwerte denen entsprechen,

die bei Belastung von 1 %, einer Temperatur von 25°C, einem Frequenzbereich von 0,1 bis 100 rad/s und einem Abstand von 1000 μm gemessen werden.

5 Revendications

1. Dispositif pour l'administration transdermique de médicament à un individu à travers une surface corporelle, comprenant : un réservoir comprenant au moins un médicament, activateur de la perméation et un polymère d'acrylate, dans lequel le réservoir est d'une composition ayant une complaisance de fluage de $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$ à $2 \times 10^6 \text{ cm}^2/\text{dyn}$ si le réservoir était sans médicament et sans activateur de la perméation, de telle sorte que le polymère d'acrylate a un composant monomère mou ne dépassant pas plus de 60 % en poids, le composant monomère mou constitué de monomères dont la T_g de l'homopolymère est de -80 °C à -10 °C, le polymère d'acrylate ayant 40 % en poids ou plus d'un composant monomère dur au moins une partie de celui-ci est un monomère polaire fonctionnel dur, le composant monomère dur constitué de monomères comportant une T_g de l'homopolymère de 0 °C à 250 °C, le monomère fonctionnel polaire consistant en des monomères qui contiennent des groupes fonctionnels de liaison hydrogène choisis parmi les groupes hydroxyle, carboxyle et amino, dans lequel le composant monomère dur est choisi parmi au moins l'un de l'acrylate d'hydroxyéthyle, l'acide acrylique, l'acétate de vinyle et le t-octylacrylamide, et le polymère d'acrylate a de 10 à 40 % en poids de composant monomère polaire fonctionnel au moins une partie de celui-ci est un monomère polaire fonctionnel dur, le polymère d'acrylate constituant 45 à 80 % en poids du réservoir et capable de maintenir l'ensemble médicament et activateur de perméation à une quantité dissoute d'au moins 30 % en poids, et ayant une T_g supérieure à -15 °C si sans activateur de perméation et sans médicament, le réservoir étant applicable en tant qu'adhésif sensible à la pression à la surface du corps pour une administration transdermique, où lesdites valeurs de T_g sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min et les valeurs de complaisance de fluage indiquées sont telles que mesurées à une tension de 1000 dyn/cm^2 , à une température de 30 °C pendant 3600 secondes et un écart de 1000 μm .
2. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend au moins l'un d'un monomère polaire fonctionnel avec un groupe hydroxyle et un monomère fonctionnel polaire avec un groupe acide carboxylique.
3. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend un copolymère acrylique résultant de (i) 40 à 50 % en poids du composant monomère acrylate d'alkyle mou, dans lequel chaque monomère acrylate d'alkyle mou ayant une T_g de l'homopolymère de -80 à -20 °C et (ii) 40 à 60 % en poids du composant monomère dur qui n'est pas également un composant monomère polaire fonctionnel, dans lequel chaque monomère dur ayant une T_g de l'homopolymère de 0 à 250 °C, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min.
4. Dispositif selon la revendication 3, dans lequel le composant de monomère d'acrylate d'alkyle est un monomère acrylate d'alkyle mou ayant 4 à 10 atomes de carbone dans le groupe alkyle.
5. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend 40 à 50 % en poids du composant monomère d'acrylate d'alkyle mou ayant une T_g de l'homopolymère inférieure à -20 °C, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min.
6. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend 40 à 50 % en poids du composant monomère d'acrylate d'alkyle mou ayant une T_g de l'homopolymère inférieure à -20 °C, le composant monomère dur ayant une T_g de l'homopolymère supérieure à 20 °C, et le monomère polaire fonctionnel ayant un groupe acide, dans lequel les valeurs de T_g indiquées sont mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min.
7. Dispositif selon la revendication 1, dans lequel l'activateur de la perméation et le médicament sont dissous dans le polymère d'acrylate et le polymère d'acrylate a une T_g de 0 à -15 °C, si sans le médicament dissous et l'activateur de perméation, tandis que le réservoir avec le médicament dissous et l'activateur de perméation a une complaisance de fluage de moins de $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$ et le module de conservation de $1 \times 10^5 \text{ dyn/cm}^2$ à $8 \times 10^5 \text{ dyn/cm}^2$, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min, les valeurs de complaisance de fluage indiquées sont telles que mesurées à une tension de 1000 dyn/cm^2 , une température de 30 °C pendant 3600 secondes et un écart de

1000 μm , et les valeurs de module de stockage indiquées sont telles que mesurées à une tension de 1 %, une température de 25 °C, une fréquence comprise entre 0,1 et 100 rad/s, et un écart 1000 μm .

- 5 8. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend un composant monomère modifiant dur ayant une T_g de l'homopolymère de 40 à 100 °C, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10°C/min.
- 10 9. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate possède un groupe hydroxyle et un groupe acide dans celui-ci et comprend un composant monomère non fonctionnel dur de 5 à 15 % en poids.
- 15 10. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate a des composants monomères composés essentiellement de 50 à 60 % en poids d'acétate de vinyle, de 10 à 20 % en poids d'acrylate d'hydroxyéthyle, et de 20 à 40 % en poids d'acrylate de 2-éthylhexyle.
- 20 11. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate comprend un monomère polaire fonctionnel choisi dans le groupe constitué par l'acide acrylique, l'acrylate d'hydroxyéthyle et l'acrylate d'hydroxypropyle.
- 25 12. Dispositif selon la revendication 1, dans lequel l'activateur de perméation et le médicament sont dissous dans le polymère d'acrylate et le polymère d'acrylate a une T_g de 0 à -15 °C, si sans l'activateur de perméation et le médicament dissous, tandis que le polymère d'acrylate avec le médicament et l'activateur de perméation dissous le polymère d'acrylate forme un réservoir ayant une T_g de -10 à -20 °C, une complaisance de fluage de moins de $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$ et un module de stockage de $1 \times 10^5 \text{ dyn/cm}^2$ à $8 \times 10^5 \text{ dyn/cm}^2$, dans lequel les valeurs de T_g indiquées sont mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min, les valeurs complaisance de fluage énoncées sont telles que mesurées à la tension de 1000 dyn/cm², une température de 30 °C pendant 3600 secondes et un écart de 1000 μm , et les valeurs du module de stockage indiquées sont telles que mesurées à une tension de 1 %, une température de 25 °C, une gamme de fréquence de 0,1 à 100 rad/s, et un écart de 1000 μm .
- 30 13. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate a une T_g de 0 à -15 °C si sans médicament et activateur de perméation, tandis que le polymère d'acrylate ayant un médicament et un activateur de perméation au dessus de 30 % en poids dans une seule phase forme un réservoir ayant une T_g de -10 à -20 °C, une complaisance de fluage de $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ à $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ et le module de conservation de $1 \times 10^5 \text{ dyn/cm}^2$ à $8 \times 10^5 \text{ dyn/cm}^2$, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min, les valeurs de complaisance de fluage énoncées sont mesurées à une tension de 1000 dyn/cm², une température de 30 °C pendant 3600 secondes et un écart de 1000 μm , et les valeurs de module de stockage indiquées sont mesurées à la tension de 1 %, une température de 25 °C, une gamme de fréquence de 0,1 à 100 rad/s, et un écart de 1000 μm .
- 35 14. Dispositif selon la revendication 1, dans lequel le polymère d'acrylate a une T_g de 0 à -15 °C, le module de stockage $8 \times 10^5 \text{ dyn/cm}^2$ ou au-dessus si sans médicament et activateur de perméation, tandis que le polymère d'acrylate avec le médicament et à l'activateur de perméation au-dessus de 30 % en poids dissous dans celui-ci forme un réservoir ayant une T_g de -10 à -40 °C, une complaisance de fluage de $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$ à $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$ et le module de stockage de $1 \times 10^5 \text{ dyn/cm}^2$ à $8 \times 10^5 \text{ dyn/cm}^2$, dans lequel les valeurs de T_g énoncées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min, les valeurs de complaisance de fluage énoncées sont telles que mesurées à la tension 1000 dyn/cm², une température de 30 °C pendant 3600 secondes et un écart de 1000 μm , et les valeurs de module de stockage indiquées sont telles que mesurées à une tension de 1 %, une température de 25 °C, une gamme de fréquence de 0,1 à 100 rad/s, et un écart de 1000 μm .
- 40 15. Dispositif selon la revendication 1, comprenant un médicament choisi dans le groupe constitué du fentanyl, du fentanyl analogue, de la galantamine et de la norelgestromine.
- 45 16. Procédé de fabrication d'un réservoir pour l'administration de médicaments par voie transdermique, comprenant : la fourniture d'un polymère d'acrylate ayant une complaisance de fluage de $7 \times 10^{-5} \text{ cm}^2/\text{dyn}$ à $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$ sans médicament et sans activateur de perméation, de telle sorte que le polymère d'acrylate a un composant monomère mou ne dépassant pas 60 % en poids, dans lequel le composant monomère mou est constitué de monomères ayant une T_g de l'homopolymère de -80 °C à -10 °C, le polymère d'acrylate ayant un composant de monomères dur de
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- 55

40 % en poids ou plus, le composant monomère dur du polymère d'acrylate comprenant des monomères ayant une T_g de l'homopolymère de 0 °C à 250 °C, dans lequel au moins une partie du monomère dur est un monomère fonctionnel polaire dur, dans lequel le monomère polaire fonctionnel est constitué de monomères qui contiennent des groupes fonctionnels de liaison d'hydrogène choisis parmi les groupes hydroxyle, carboxyle et amino, dans lequel le composant de monomère dur est choisi parmi au moins l'un d'hydroxyéthyle d'acrylate, l'acide acrylique, l'acétate de vinyle et le t-octylacrylamide, le polymère d'acrylate capable de contenir une combinaison d'activateur de perméation et un médicament dans le polymère d'acrylate à une quantité dissoute d'au moins 30 % en poids, en incorporant l'activateur de perméation et le médicament dans le polymère d'acrylate pour aboutir à un réservoir d'une seule phase de sorte que le médicament et l'activateur de perméation dissous constituent ensemble plus de 20 % en poids, et le polymère d'acrylate constituant 45 % en poids à 80 % en poids en matières solides du réservoir, dans lequel le réservoir est applicable comme adhésif autocollant à la surface du corps, dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) à une vitesse de chauffage de 10 °C/min et les valeurs de complaisance de fluage indiquées sont telles que mesurées à une tension de 1000 dyn/cm², une température 30 °C pendant 3600 secondes et un écart de 1000 μm.

17. Procédé selon la revendication 16, dans lequel le réservoir avec le médicament et l'activateur de perméation dissous a une température de transition vitreuse T_g inférieure à -10 °C tandis que le polymère d'acrylate sans médicament et sans amplificateur de perméation a une T_g supérieure à -15 °C, dans lequel des valeurs de T_g indiquées sont mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min.

18. Procédé selon la revendication 16, dans lequel le polymère d'acrylate comprend (i) 40 à 50 % en poids du composant monomère mou acrylate d'alkyle, dans lequel chaque monomère acrylate d'alkyle mou ayant à l'intérieur une T_g de l'homopolymère de -80 à -20 °C, (ii) 40 à 60 % en poids de composant monomère dur qui n'est pas également un composant monomère polaire fonctionnel, dans lequel chaque composant de monomère dur ayant une T_g de l'homopolymère de 0 à 250 °C, et (iii) 10 à 40 % en poids de composant monomère polaire fonctionnel, dans lequel le monomère mou est un monomère acrylate d'alkyle ayant 4 à 10 atomes de carbone dans le groupe alkyle, dans lequel les valeurs de T_g indiquées sont mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min.

19. Procédé selon la revendication 16, dans lequel le polymère d'acrylate a une T_g de 0 à -15 °C si sans médicament et activateur de perméation, et le réservoir avec le médicament et activateur de perméation dissous a une T_g de -10 à -20 °C, une complaisance de fluage de 1×10^{-4} cm²/dyn à 6×10^{-4} cm²/dyn et le module de stockage de 1×10^5 dyn/cm² à 8×10^5 dyn/cm², dans lequel les valeurs de T_g indiquées sont telles que mesurées par analyse calorimétrique à compensation de puissance (ACD) avec une vitesse de chauffage de 10 °C/min, les valeurs de complaisance de fluage énoncées sont mesurées à une tension de 1000 dyn/cm², une température de 30 °C pendant 3600 secondes et un écart de 1000 μm, et les valeurs de module de stockage indiquées sont comme évaluées à la tension de 1 %, la température de 25 °C, une gamme de fréquence de 0,1 à 100 rad/s, et un écart de 1000 μm.

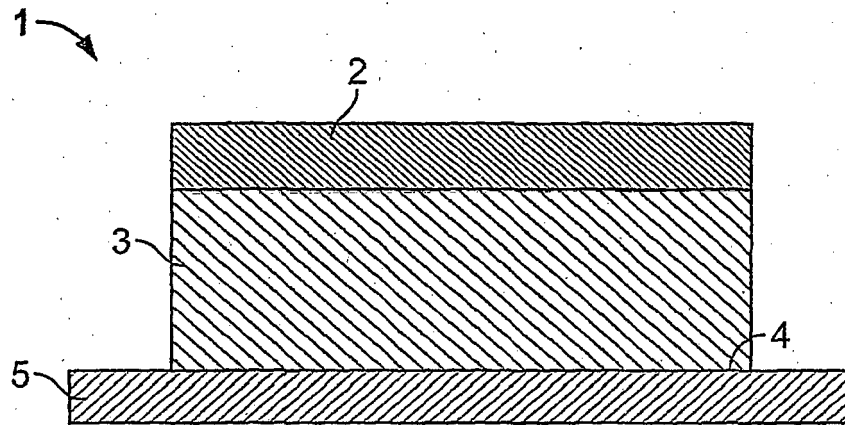


FIG. 1

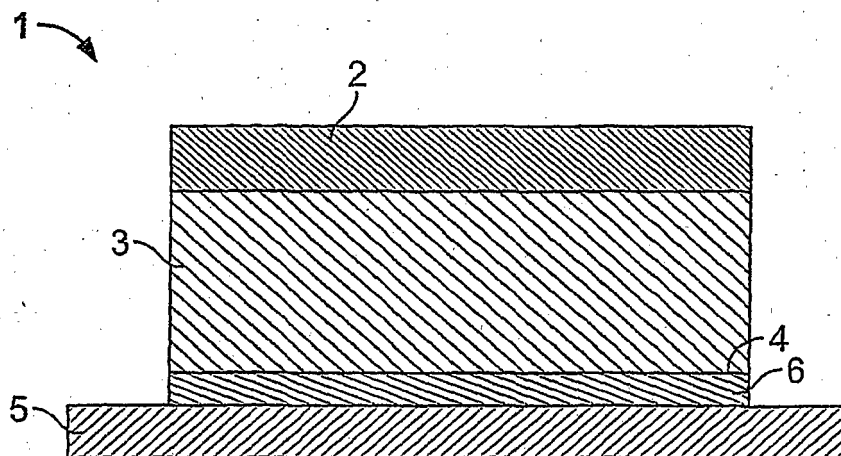


FIG. 2

REFERENCES CITED IN THE DESCRIPTION

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